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Metal-Catalyzed C(sp^2)–H Functionalization Processes of Phenylalanine- and Tyrosine-Containing Peptides

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The site-selective chemical diversification of biomolecules constitutes an unmet challenge of capital importance within medicinal chemistry and chemical biology. The functionalization of otherwise unreactive C–H bonds holds great promise for reducing the reliance on existing functional groups, thereby streamlining chemical syntheses. Over the last years, a myriad of peptide labelling techniques featuring metal-catalyzed C–H functionalization reactions have been developed. Despite the wealth of reports in the field, the site-selective modification of both phenylalanine (Phe) and tyrosine (Tyr) compounds upon metal catalysis remain comparatively overlooked. This review highlights these promising tagging strategies, which generally occur through the formation of challenging 6-membered metallacycles and enable the late-stage diversification of peptides in a tailored fashion.

1. Introduction

Amino acids and peptides derived thereof are privileged and versatile compounds of paramount importance in organic chemistry, chemical biology, and drug discovery. They are prevalent motifs in a high number of drug candidates[1] and have shown to be powerful catalysts to perform a wide range of chemical reactions in an enantioselective fashion,[2] and effective ligands in the realm of metal-catalyzed C–H functionalization.[3] Furthermore, it has been demonstrated that increasing the steric bulk of the side-chains of amino acids within a peptide sequence often results in higher metabolic resistance of the corresponding biomolecule to enzyme degradation as well as in improved biological activity and pharmacokinetics.[4] As a result, the post-assembly modification of peptides and proteins in a tailored manner represents a prime challenge of widespread interest in the burgeoning field of bioconjugation.[5] With the rapid advances in protein engineering, the synthetic toolbox to label amino acids and peptides is ever-expanding within the last decade. However, despite the advances realized, among the 20 proteinogenic amino acids only a very limited number stand out as appropriate targets for the development of reliable bioconjugation methods.

Owing to the high nucleophilicity under physiological conditions of the thiol and amine motifs within cysteine (Cys) and lysine (Lys) residues, respectively, most tagging techniques exploit their innate reactivity to assemble engineered proteins in a site-specific manner.[5] Conversely, the modification of poorly nucleophilic or hydrophobic residues has been comparatively less explored and hence the development of new innovative post-modifications of peptides still represents a pressing goal within the field.

C–H functionalization has changed the landscape of synthetic chemistry enabling the direct manipulation of otherwise unreactive hydrocarbon moieties in a straightforward manner, thus minimizing the chemical waste by avoiding the use of pre-functionalized compounds.[6] Remarkably, the last years have witnessed the upsurge of a myriad of chemical processes featuring innovative bond disconnections, which resulted in the synthesis of peptides and proteins that are beyond the reach of traditional methods. In particular, metal catalysis has recently unlocked new tactics in the field, thereby providing streamlined techniques toward the manipulation of C–H bonds embedded within the amino acid backbone[7] and the corresponding side-chains.[8] Driven by the exponential growth of C(sp^2)–H functionalization reactions within simple aryl systems, a variety of site-selective methods for the modification of aromatic residues such as tryptophan (Trp)[9] have been devised by harnessing the innate reactivity of its indole ring. Indeed, the oxidative coupling of Trp and tyrosine (Tyr) residues constitutes a crucial step within the biosynthesis of a sheer number of natural products.[10] In stark contrast, the modification of typically inert C(sp^2)–H bonds within phenylalanine (Phe) has been overshadowed and comparatively less studied.[11] The site-selective modification of the hydrophobic phenyl side chains relies on two general strategies: a) the installation of an external directing group (DG) at the terminal amino group, or b) the use of the peptide backbone, which could act as either an effective *N,N*-bidentate endogenous ligand or as an *N,O*-ligand when using terminal unprotected carboxylic acids. In both cases, upon the formation of the

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corresponding metallacycle the modification of the δ-C(sp^2)–H bond of the Phe residue can occur in a selective fashion (Scheme 1). In both cases, the most frequently invoked mechanistic scenario features a Pd(II)/Pd(IV) catalytic cycle.

With the aim to complement the latest reviews on the topic,[7,8,11] herein we will describe the latest advances in the site-selective C(sp^2)–H functionalization of Phe-containing peptides featuring the use of metal catalysis. Likewise, the few related metal-catalyzed reactions available with the parent Tyr-containing derivatives occurring upon an inner-sphere mechanism will be also discussed.[12] Accordingly, metal-free reactions as well as the modification of Phe and Tyr residues at their benzylic C(sp^3)–H bond will be beyond the scope of this user guide. This review will focus on appraising existing methodologies up to early 2021 and, when applicable, key aspects of the underlying reaction mechanisms entailing organometallic species will be detailed.

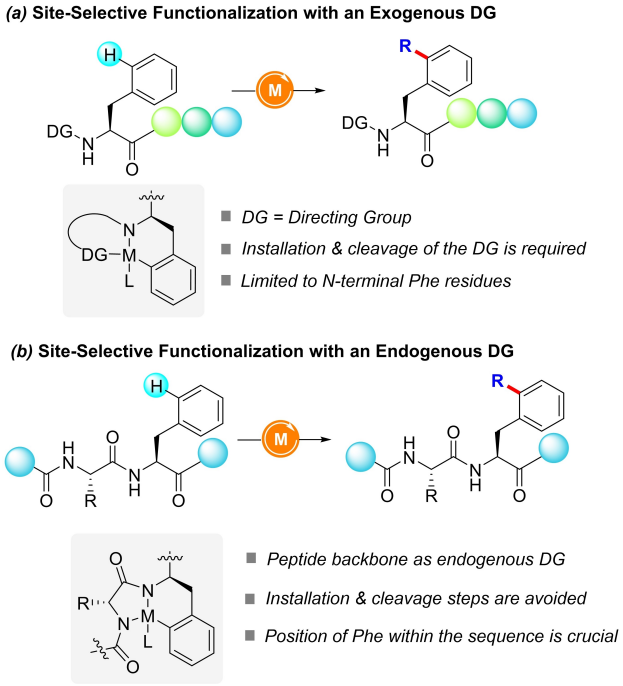
2. C–C Bond-Forming Reactions

In this section, metal-catalyzed *ortho*-C–H functionalization reactions wherein a carbon-moiety is introduced into the phenyl ring within Phe and Tyr residues will be disclosed.

2.1. C–H Arylations

One of the most exploited metal-catalyzed tagging techniques within a peptide sequence involves the Pd-catalyzed C–H arylation reaction with aryl halides through a Pd(II)/Pd(IV) regime. The latter has been described to site-selectively occur both at the C2 site of indoles within Trp-containing peptides[9] and at the C(sp^3)–H of aliphatic side-chains[8b,c] of Ala, Val or even Phe residues.[13] However, the analogous process occurring at the δ-C(sp^2)–H bonds within the phenyl ring of Phe or Tyr units has been comparatively unexplored.

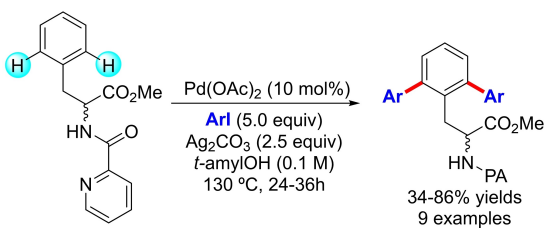
Arkaitz Correa was born in Bilbao in 1979. He studied chemistry at the University of the Basque Country (UPV/EHU), where he completed his PhD studies in November 2006 under the guidance of Prof. Esther Domínguez. Along that time, he did a 3-month stay with Prof. Ben L. Feringa at the University of Groningen. In January 2007, he undertook his first postdoctoral studies with Prof. Carsten Bolm at RWTH Aachen University (2007–2008) funded by the Basque Government. Subsequently, he joined the group of Prof. Ruben Martin at ICIQ (Tarragona) as a postdoctoral fellow (2008–2010) and as a "Juan de la Cierva" researcher (2011–2014). In April 2014, he started his independent career at UPV/EHU as a "Ramón y Cajal" fellow. In December 2019, he was tenured to Associate Research Professor at the UPV/EHU. His group is focused on the development of metal-catalyzed C–H functionalization reactions toward the modification of peptide derivatives. Along the last years, he has received the GEQO Young Scientist Award 2019 and the Thieme Chemistry Journal Award 2020.



Scheme 1. δ-C(sp^2)–H functionalization of Phe derivatives.

In 2018 Jiang and co-workers reported the first *ortho*-diarylation of a racemic Phe unit housing the picolinamide (PA) as the *N*-terminal DG.[14] In the presence of Ag_2CO_3 and *tert*-amylOH as solvent at 130 °C PA-Phe-OMe successfully underwent the corresponding Pd-catalyzed diarylation reaction with aryl iodides (Scheme 2). The arylation manifold was not applied neither in an enantiomerically pure Phe unit nor in Phe-containing peptides. However, it demonstrated the feasibility of performing a remote C–H arylation process upon the intermediacy of a challenging 6-membered palladacycle with the aid of a bidentate DG, and set the basis for further discoveries in the field.

In connection with their studies on *meta*-C–H arylation reactions,[15] the Yu group reported a challenging ligand-enabled *meta*-selective Pd-catalyzed C–H arylation platform featuring norbornene (NBE) as a transient mediator of protected

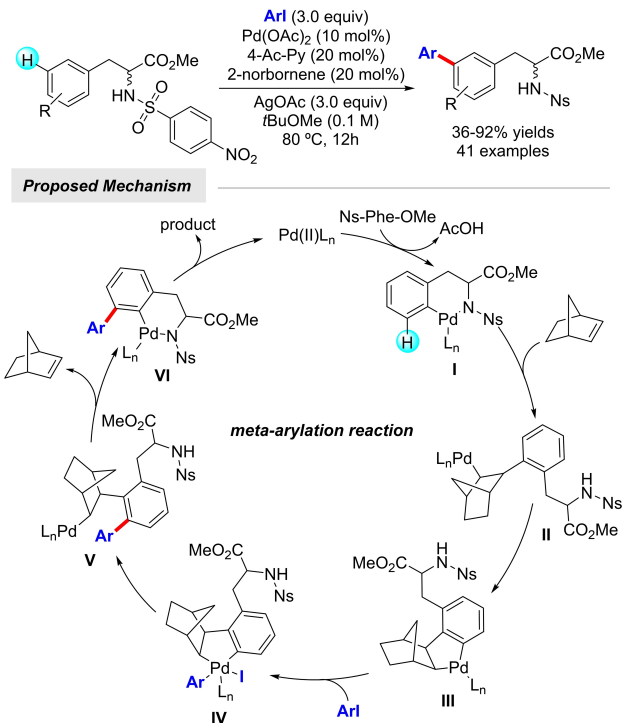


Scheme 2. δ-C(sp^2)–H diarylation of PA-Phe-OMe with ArI.

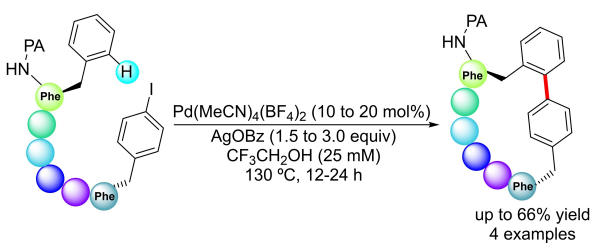
amines including a wide range of simple *N*-nosyl Phe compounds.[16] After evaluating a number of pyridine-based ligands, they observed that its presence was required for the process to occur and the use of 4-acetylpyridine resulted in the highest yields. Unlike other Catellani reactions,[17] NBE could be used in a catalytic fashion in the presence of 3.0 equivalents of AgOAc without affecting the catalyst performance. Although HPLC analysis with the simple Ns-Phe-OMe derived from enantiomerically pure L-Phe verified that no racemization took place along the reaction, the synthetic scope was evaluated with racemic Phe compounds (Scheme 3). When using natural unsubstituted Phe residues, the corresponding diarylated compound was obtained; however, the use of both *ortho*- or *meta*-substituted Phe derivatives ushered in a selective mono-arylation reaction and the process was found compatible with a wide range of aryl and heteroaryl iodides. Importantly, β-nosyl protected Phe-containing dipeptides could be also accommodated, the reaction was found scalable and the required nosyl group could be easily cleaved. Based on previous reports within the field, they proposed a plausible reaction mechanism. The reaction would start with the palladation of the Ns-Phe derivative, and the so-formed palladacycle **I** was proposed to react with NBE to deliver intermediate **II**. The latter could undergo a subsequent palladation, thereby resulting in the formal *meta*-C–H activation of the Ph ring. Next, oxidative addition of the corresponding ArI would afford a highly reactive Pd(IV) intermediate (**IV**), which upon reductive elimination and subsequent β-carbon elimination of NBE would furnish the *meta*-arylated product and regenerate the active Pd(II) catalyst.

Owing to their improved cell penetration ability and higher metabolic stability comparing with their acyclic analogues, cyclopeptides are lately gaining increasing attention and are coveted compounds within the field of drug discovery and medicinal chemistry.[18] Common macrocyclization reactions involve head-to-tail lactamizations, disulfide formation or multi-component reactions, among others. Driven by the advent of metal-catalyzed C–H functionalization reactions as an enabling tool for the modification of peptides, new topological architectures have been forged upon innovative peptide-stapling techniques.[19] The first example featuring the assembly of cyclopeptides through a Pd-catalyzed C–H functionalization reaction was reported by Albericio and Lavilla in 2015.[20] In those early examples, unnatural iodinated Phe residues could be coupled in an intramolecular fashion with Trp units, thereby providing unique Phe-Trp cross-linkages. Likewise, in 2017 the parent process to couple iodinated Phe units with amino acids housing aliphatic side-chains such as Ala or Leu residues was described by Albericio[21a] and Wang.[21b] More recently, Chen and co-workers have reported a picolinamide-directed Pd-catalyzed intramolecular arylation platform wherein new biaryl linkages were assembled between iodinated Phe residues and natural Phe units.[22a] This platform enabled the synthesis of a new family of cyclopeptides of high structural complexity upon an intramolecular δ-arylation reaction (Scheme 4). Likewise, the iodinated Phe residue could be successfully coupled with other non-natural phenylglycine or allylglycine units as well as with the aliphatic side-chain of Val units.[22b] In those cases, the proposed mechanism would involve the formation of a 5-membered palladacycle prone to react with the aryl iodide in an intramolecular fashion, thus delivering a high valent Pd(IV) intermediate. The latter would ultimately undergo a reductive elimination to provide the corresponding cyclopeptide and the active Pd(II) catalyst. Conversely, when starting from the parent Phe residue a 6-membered palladacycle would be formed.

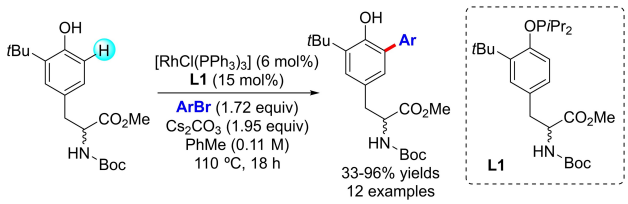
Tyr residue within proteins easily undergoes Single Electron Transfer (SET) events under oxidative conditions, thus producing highly reactive tyrosyl radical species prone to undergo a variety of chemical reactions including dimerizations to form biaryl compounds upon radical-radical couplings.[23] In stark contrast, the arylation reaction of Tyr through an inner-sphere mechanism entailing organometallic species has been scarcely studied. In fact, a high number of C–H functionalization reactions have been explored within simple phenol compounds but their extension to Tyr-containing peptides still remains



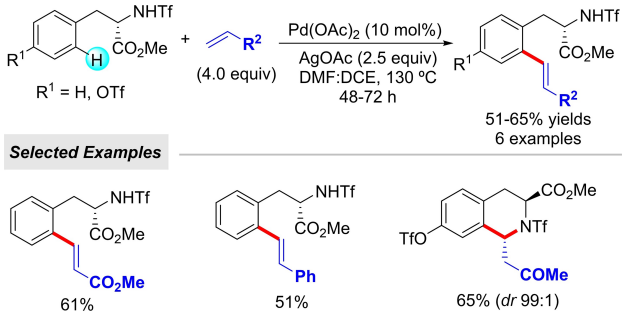
Scheme 3. *meta*-C(sp²)–H arylation of Ns-Phe derivatives.



Scheme 4. Intramolecular δ-C(sp²)–H arylation.



Scheme 5. Rh-catalyzed arylation of a Tyr compound.



Scheme 6. Olefinations using triflamide as DG.

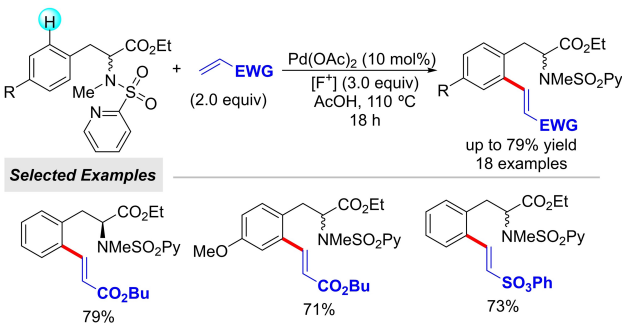
elusive. In 2009 Bedford and co-workers reported a Rh-catalyzed arylation of racemic Boc-Tyr-OMe housing a *tert*-butyl group at C6 in order to inhibit the corresponding diarylation process.[24] A variety of aryl bromides could be used in the presence of Wilkinson catalyst [$RhCl(PPh_3)_3$] and a phosphinite ligand bearing a Tyr residue. Control experiments to *in situ* form the corresponding phosphinite ligand were unsuccessful, which may indicate the presumable competitive coordination of the amino functionality (Scheme 5). The reaction was proposed to follow a similar pathway to that proposed for the arylation of simple phenol systems. Accordingly, a base-assisted *ortho*-metallation directed by the supporting ligand could render a rhodacycle, which would next undergo the oxidative addition of the ArBr. Eventually, reductive elimination and transesterification would deliver the corresponding 2-arylated Tyr compound. The required *tert*-butyl group could be cleaved and performed a subsequent arylation reaction to obtain unsymmetrically substituted diarylated Tyr derivatives.

2.2. C–H Olefinations and Alkynylations

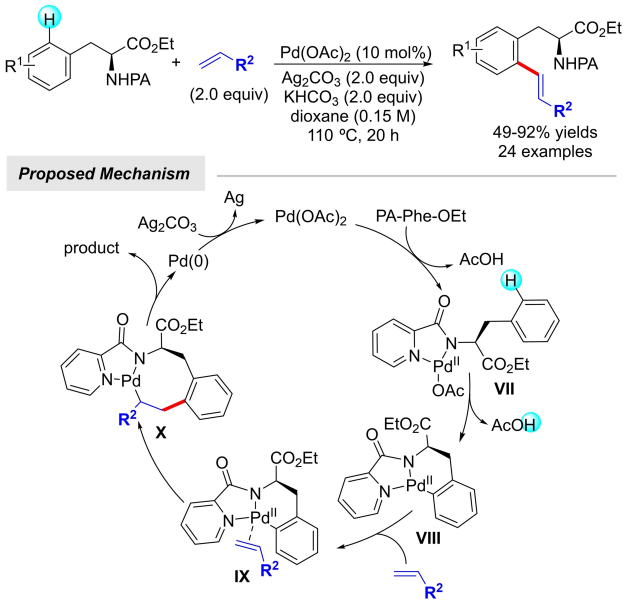
The Fujiwara-Moritani reaction represents a valuable synthetic tool, which enables the installation of olefins into non-prefunctionalized arenes in the presence of an oxidant. In 2008 the Yu group developed a number of Pd-catalyzed C–H functionalization reactions with arylethylamines featuring the use of trifluoromethylsulfonamide as efficient DG.[25] Among a number of amine-protected compounds, the triflamide group offered an optimal interplay between the required acidity of the amine motif to bind with the Pd center and a sufficient electrophilicity of the resulting palladacycle to undergo further C(sp^2)–H functionalization reactions (Scheme 6). Accordingly, in the presence of AgOAc as oxidant, both acrylates and styrenes could be efficiently installed at the δ-position within Phe and Tyr residues. When using highly reactive acrylate, the addition of NaH_2PO_4 was required to suppress the diolefination reaction. Importantly, the use of related vinyl ketones resulted in a tandem olefination/aza-Michael addition, which furnished tetrahydroquinolines in a highly diastereoselective fashion.

Driven by the successful use of sulfonylpyridine motif as efficient DG,[26a] Carretero and co-workers reported the olefination of a variety of Phe compounds housing the *N*-methyl-*N*-sulfonylpyridine (*N*-$MeSO_2Py$) as optimal DG.[26b] In the presence of *N*-fluoro-2,4,6-trimethylpyridinium triflate [F^+] as oxidant a wide range of activated olefins could be site-selectively incorporated into the Phe or even Tyr framework (Scheme 7). Although the process was demonstrated to happen with minimal erosion of the enantiomeric purity, the synthetic scope was evaluated in racemic compounds. Importantly, the cleavage of the DG ushered in the assembly of tetrahydroisoquinolines upon a tandem deprotection/aza-Michael reaction with good diastereocontrol.

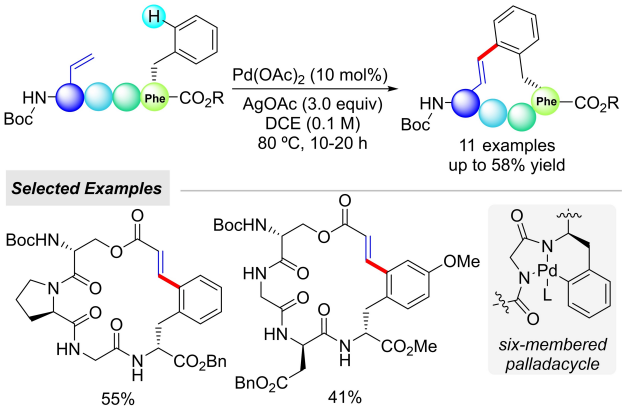
In 2017 a complementary method developed by Zhao and co-workers featuring the use of PA as DG enabled the selective appendance into simple Phe compounds of numerous olefins including activated alkenes such as acrylates, vinyl sulfones, phosphates and ketone derivatives but also unactivated aliphatic alkenes such as 1-hexene, among others.[27] Whereas the use of natural unsubstituted or *para*-substituted Phe compounds and high excess of the corresponding alkenes resulted in the exclusive formation of the diolefinated products, the presence of *ortho*- and *meta*-substituents within the aryl ring ushered in the preferential mono-olefination event. The PA could be easily cleaved, and the reaction was scalable. Unfortunately, the method could not be applied in a more challenging peptide setting. Although mechanistic experiments were not performed, a plausible reaction pathway was proposed based on existing precedents on other oxidative Heck reactions (Scheme 8). After coordination of the Pd(II) with the bidentate PA and subsequent *ortho*-metallation, the resulting 6-membered palladacycle (VIII) could undergo a migratory insertion of the corresponding olefin. The final product would be obtained upon a β-H elimination event, thereby releasing Pd(0) which could be reoxidized with the aid of Ag_2CO_3.



Scheme 7. Olefinations using $NMeSO_2Py$ as DG.



Scheme 8. Olefinations using PA as DG.



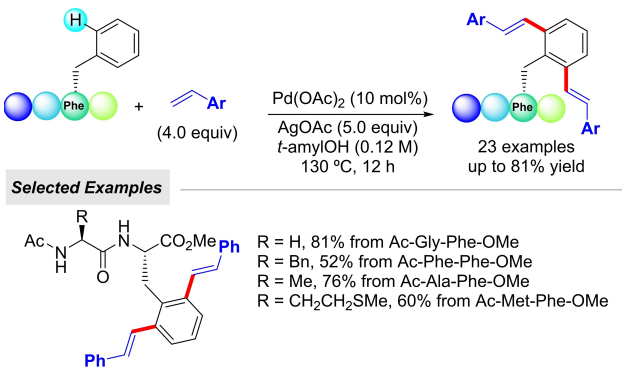
Scheme 9. Backbone-directed peptide macrocyclization.

Despite the common practice of an exogenous DG in the realm of C–H functionalization, the major downside comes from the often long synthetic sequence involving its installation and further cleavage. In this regard, a major breakthrough within the field was achieved by the group of Yu, who harnessed the peptide backbone as an efficient and endogenous DG to develop a variety of C–H functionalization reactions.[28] Encouraged by these excellent results, Wang and co-workers implemented this promising tactic to forge challenging cyclopeptides through macrocyclization techniques between benzosulfonamides and olefins.[29] Likewise, they developed elegant and highly robust late-stage Pd-catalyzed olefination reactions for the assembly of cyclic peptides housing a unique aryl-alkene cross-linkage.[30]

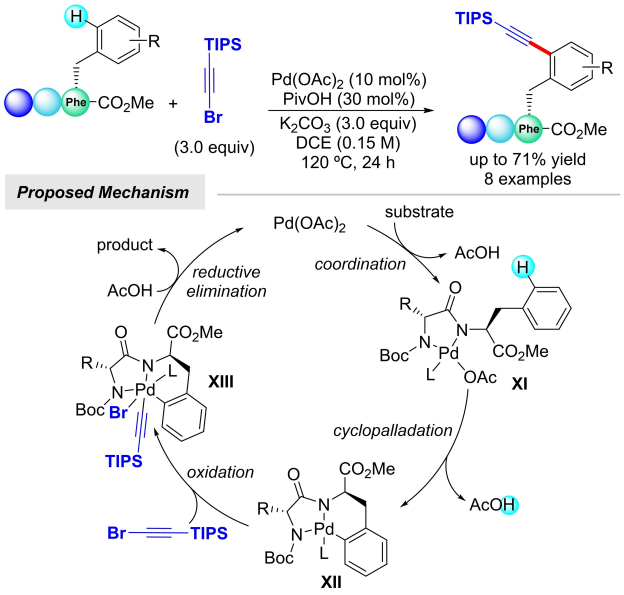
They initially demonstrated the feasibility of intermolecular olefination reactions between dipeptides and a variety of olefins upon leveraging the peptide backbone as effective DG. Control experiments revealed that the success of the process was dependent on the use of peptide backbone amides, which are *N*-terminal to the corresponding Phe unit. Importantly, the method enabled chemical ligation in a straightforward fashion with Phe-containing peptides and olefins derived from the corresponding Ser-containing peptide. Notably, the method could be used for the assembly of a wide range of cyclopeptides of high structural complexity. The macrocyclization could only occur in the *N*-to-*C* direction and at least two amide bonds in adjacent position to the *N*-terminal Phe residue were required to bind with the metal catalyst, thereby forming a 6-membered palladacycle. The method was also applied for the cyclization of a Tyr-containing sequence (Scheme 9). More recently, the latter δ-C(sp^2)–H olefination processes with acrylates have been achieved featuring the use of an oxazole motif as alternate endogenous DG. Importantly, alkenes derived from bioactive molecules could be ligated to Phe and Tyr-containing peptides.[31]

Capitalizing the peptide backbone as an efficient DG, Cross and co-workers developed a practical diolefination reaction with styrenes in the presence of 5.0 equivalents of AgOAc.[32] A wide variety of styrenes smoothly underwent the target difunctionalization process in Phe-containing di-, tri- and tetrapeptides (Scheme 10). Control experiments evidenced the crucial role of the amide bonds as the use of phthalimide as *N*-protecting group resulted in the inhibition of the process and, as observed by Wang,[30] the position of the Phe unit within the peptide sequence was determinant in the reaction outcome.

Song and co-workers independently developed an analogous intermolecular olefination reaction assisted by the peptide backbone,[33] which was applied for the selective modification of a number of di- and tripeptides using not only styrenes but also other activated olefins and even allyl acetate as coupling partners. Whereas the preferential formation of the mono-olefinated Phe-residue was often observed, in the presence of dipeptides bearing both Met and Ser unit the corresponding diolefination was achieved in excellent yields. Unnatural Phe units bearing nitro, fluoro and chloro groups smoothly underwent the exclusive mono-alkenylation reaction. Interestingly, the challenging alkynylation reaction with (bromoethynyl)



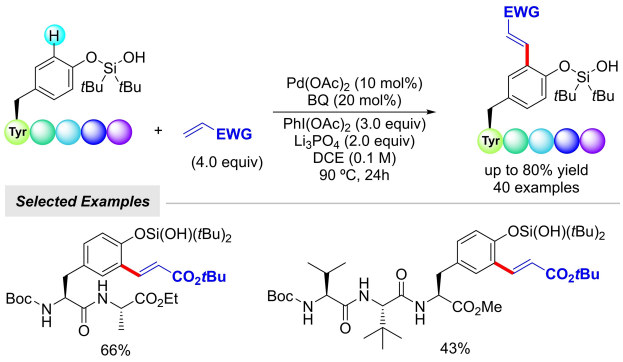
Scheme 10. Backbone-directed peptide olefination with styrenes.



Scheme 11. Backbone-directed peptide alkynylation.

triisopropylsilane upon the assistance of the peptide backbone within di- and tripeptides was also achieved (Scheme 11). The competitive difunctionalization reaction was suppressed by the use of unnatural substituted Phe-containing compounds. On the basis of literature reports, the proposed mechanism started by the coordination of $Pd(OAc)_2$ with the Phe-containing peptide forming a *N,N*-bidentante Pd-complex (**XI**). The latter could undergo a C(sp^2)–H activation event, and the so-formed 6-membered palladacycle (**XII**) would react with the corresponding alkynyl bromide to deliver a Pd(IV) intermediate (**XIII**). Finally, the latter would provide the product upon reductive elimination and the active catalyst. The parent process on simple and racemic Phe and acetyl-protected Tyr residues has been also accomplished with the aid of oxalyl amide as external DG under similar reaction conditions.[34]

Although isolated examples of the olefination of simple Tyr residues have been described within the scope of the methods described above, a general olefination reaction of Tyr-containing peptides has remained elusive during the last years. In 2019 the *ortho*-alkenylation of wide range of phenol derivatives was described under the Pd/AgOAc system.[35] Among them, a short family of racemic Tyr compounds, including the challenging native Tyr unit, were efficiently olefinated with acrylates and styrene. More recently, the Xiong group developed a robust late-stage olefination of Tyr-containing oligopeptides with activated olefins.[36] The success of the process relied on the use of a silanol group tethered to the phenol ring, which exhibited superior coordinating ability to that of the peptide backbone, and, owing to its high bulky nature, the result was the selective olefination reaction (Scheme 12). A wide variety of peptides bearing protected polar residues such as Lys, Thr, and Asp boded well with the reaction conditions. The authors hypothesized that the reaction pathway would involve the formation of a kinetically less favored 6-membered palladacycle with the



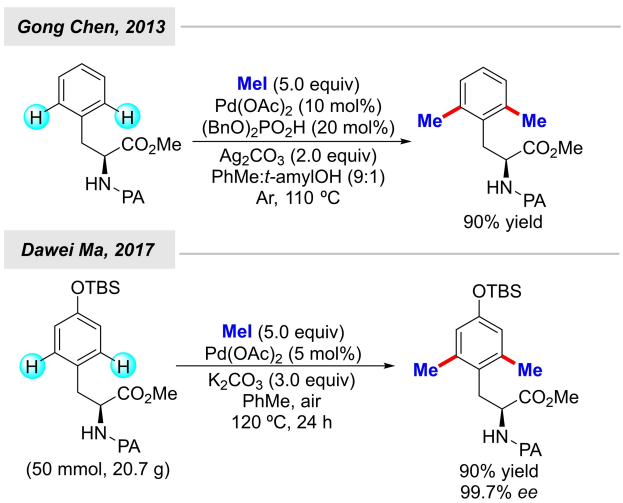
Scheme 12. Olefination of Tyr-containing peptides using silanol as DG.

corresponding silanol motif, thereby eventually providing the *ortho*-olefination products.

2.3. C–H Alkylations

As part of their work on the picolinamide-directed Pd-catalyzed C(sp^3)–H alkylation of unactivated amines with alkyl iodides, Chen and co-workers also demonstrated the feasibility of performing the dialkylation of simple PA-Phe-OMe with MeI in excellent yield through a δ-C(sp^2)–H alkylation.[37] More recently, the group of Ma developed a more practical and highly robust, yet scalable alkylation reaction of various O-protected Tyr residues under silver-free reaction conditions.[38] Among a series of DGs, PA exhibited superior coordinating ability and provided the corresponding dimethylated compounds in excellent yields (Scheme 13). The scope of these protocols concerning the alkyl coupling partner was not fully explored and their application in a more challenging peptide setting was not evaluated.

Inspired by the *meta*-arylation manifold developed by Yu,[16] Ding and co-workers reported the *meta*-alkylation of nosyl-



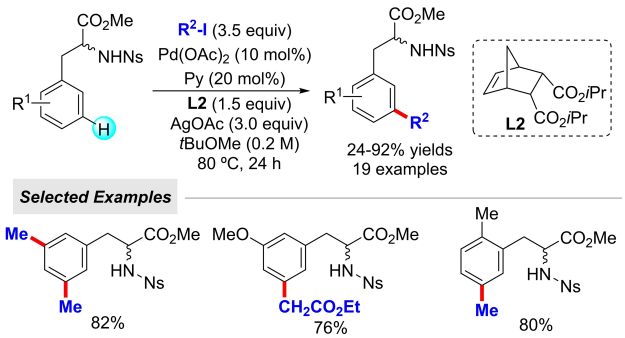
Scheme 13. Alkylation using PA as DG.

protected Phe compounds with alkyl iodides (Scheme 14).[39] A careful screening process led in this case to the use of pyridine and norbornene **L2** as the optimal chelating ligand and reaction mediator, respectively. The authors proposed an analogous reaction pathway to that proposed by Yu and the reaction was performed on racemic Phe compounds.

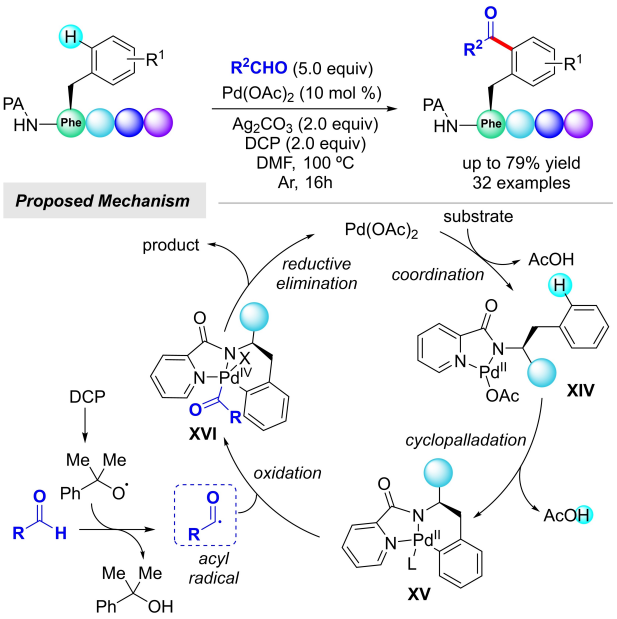
2.4. C–H Acylations

The diversification of peptides through radical chemistry has mostly involved outer-sphere mechanisms wherein the metal plays a redox-role.[7] Conversely, peptide tagging techniques upon inner-sphere radical reactions remain comparatively unexplored.[40] For instance, although radical C(sp^2)–H acylations within simple arenes upon chelation assistance has been well explored in the last decade,[41] their translation to the emerging field of bioconjugation is not trivial and the use of aldehydes as practical and versatile counterparts has been overlooked.[42] In 2019, Correa and co-workers reported for the first time a Pd-catalyzed acylation platform, which enabled the site-selective appendance of a wide range of aldehydes at the δ-C–H site of Phe-containing compounds in a radical fashion.[43] The use of a bidetante DG was crucial for the process to occur, and control experiments revealed the superior efficiency of PA, although a related carboxamide housing a 1,2,3-triazole unit could be also used in these endeavours. A wide range of aromatic, hetero-aromatic and even aliphatic aldehydes could be installed in a dehydrogenative manner to furnish the corresponding ketone derivatives. The use of dicumyl peroxide (DCP) was pivotal for the activation of the corresponding aldehyde and the addition of silver carbonate was shown to increase the yields. In general terms, preferential monoacylation was mostly achieved except when using the highly reactive 1,3,5-trimethoxybenzaldehyde, which furnished the diacylated product in high yields. Notably, the method could be used to tackle the more challenging labelling of short-to-medium peptides at the *N*-terminal Phe residue.

Interestingly, Pd complex **XIV** was isolated and its use in catalytic and stoichiometric fashion led to the target product, hence evidencing its pivotal role within the catalytic cycle (Scheme 15). Accordingly, the proposed mechanism started

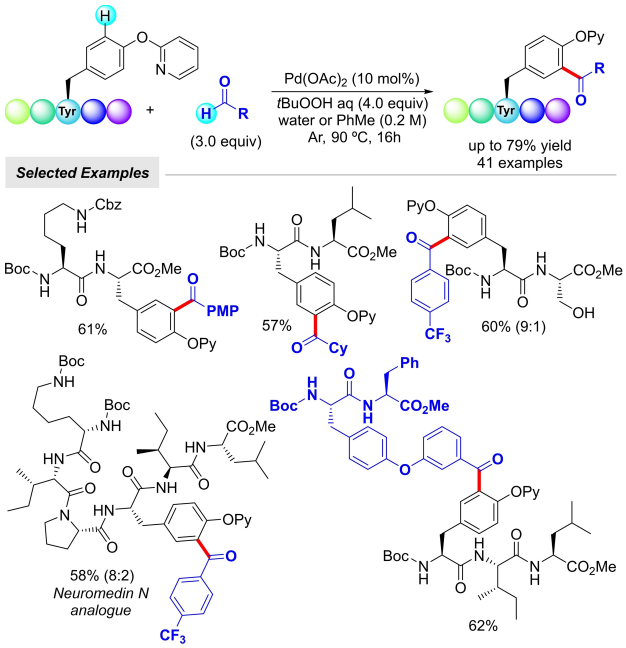


Scheme 14. *meta*-C(sp^2)–H alkylation of Ns-Phe derivatives.



Scheme 15. δ-C(sp^2)–H acylations of Phe-containing peptides.

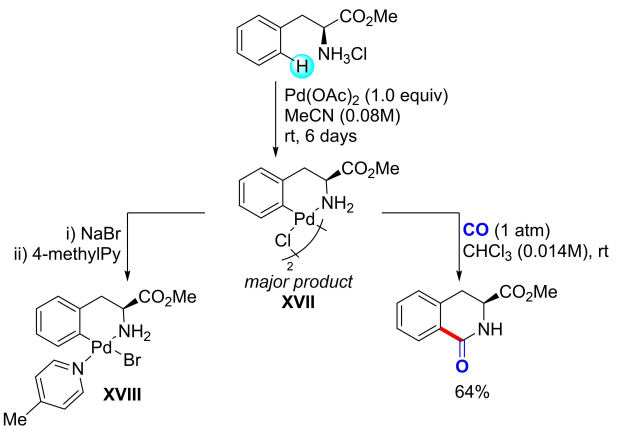
with the coordination of the picolinamide-containing Phe derivative and further *ortho*-palladation to deliver the 6-membered palladacycle (**XV**). The latter could undergo the addition of the *in situ* formed acyl radical species, thereby resulting in the formation of a transient Pd(III) species, which would be likely evolved into the corresponding Pd(IV) intermediate (**XVI**) in the oxidizing reaction conditions. Finally, reductive elimination would deliver the acylated peptide and the active Pd(II) catalyst. As in other Pd-catalyzed C–H functionalization reactions, the actual role of the silver additive remained unclear, and the authors hypothesized that it could favour either the catalyst regeneration or even any of the elemental steps upon the formation of Ag–Pd heterodimeric species.[44] Encouraged by these results, the same group expanded the synthetic toolbox for the diversification of peptides and reported a robust Pd-catalyzed radical acylation of a collection of Tyr-containing peptides with aldehydes.[45] The appendance of a pyridyl group within the oxygen atom of the Tyr ring directed the formation of a 6-membered palladacycle prone to undergo the corresponding acylation reaction. In this case, the method was found water-compatible and the addition of expensive silver salts was not required. Moreover, the installation of the DG within the phenol unit resulted in the modification of the Tyr residue, regardless of its position within the peptide sequence. Notably, a wide variety of oligopeptides of high complexity were efficiently acylated in a late-stage manner with preferential selectivity toward the mono-acylation reaction, including biologically relevant neuropeptides (Scheme 16). Importantly, the aldehyde unit could be tethered within a Tyr-containing peptide and coupled with other peptides, thereby resulting in the assembly of oligopeptides featuring a unique diaryl ketone cross-linking upon chemical ligation.



Scheme 16. δ-C(sp^2)–H acylations of Tyr-containing peptides.

2.5. C–H Carbonylations

Whereas the isolation and full characterization of palladacycles or other related metallacycle intermediates often support reliable mechanistic proposals in the field of C–H functionalization, the parent intermediates featuring an amino acid or a peptide sequence are scarce in the literature. In 2007 Vicente and co-workers reported the *ortho*-palladation of L-Phe-OMe·HCl and further chemical transformations with the isolated 6-membered-palladacycle. When mixing unprotected phenylalanine methyl ester and $Pd(OAc)_2$, they obtained a mixture of products, wherein a chloride-bridged dinuclear *ortho*-palladacycle (**XVII**) was the major compound.[46] Further treatment with NaBr and 4-picoline enabled the isolation of the mononuclear complex **XVIII** (Scheme 17). X-Ray diffraction and NMR analysis



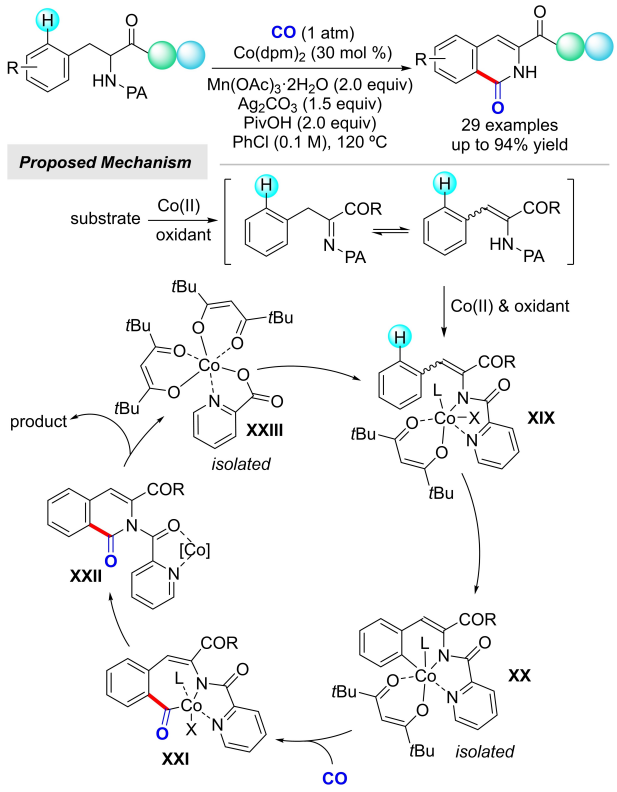
Scheme 17. Palladation of L-Phe-OMe·HCl and its carbonylation reaction.

supported a distorted-square-planar structure and a *trans* conformation of the nitrogen containing groups, which was in accordance with the structure of other palladacycles derived from simple benzylamines. Interestingly, the reaction mixture obtained from combining L-Phe-OMe·HCl with $Pd(OAc)_2$ afforded the corresponding tetrahydroisoquinoline derivative in the presence of carbon monoxide, which supported the intermediacy of a transient 6-membered palladacycle (**XVII**). Further studies by García and co-workers enabled the development of catalytic carbonylation reactions with *N*-unprotected arylethylamines.[47] However, the use of quaternary aromatic α-amino esters was crucial for the process to occur and natural Phe derivatives resulted in mixtures of the corresponding benzolactam and acyclic acetamide derivatives.

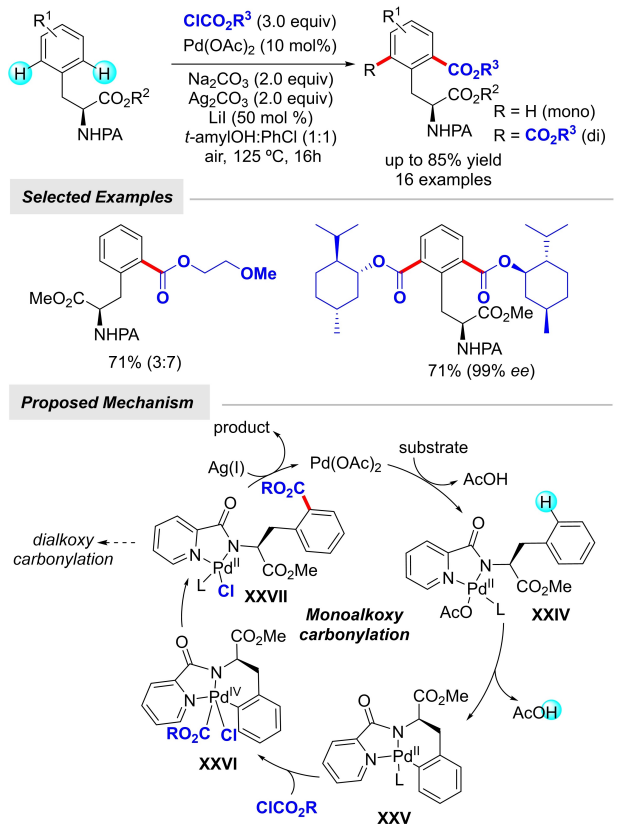
Very recently, Grigorjeva and co-workers have developed a Co-catalyzed carbonylation of Phe derivatives featuring the use of PA as a traceless DG.[48] Notably, a variety of substituted Phe compounds could be carbonylated to deliver the corresponding 1-oxo-1,2-dihydroisoquinolines in good to excellent yields, even di- and tripeptides could be employed, albeit partial racemization occurred in those cases. Control experiments underpinned the formation of an unsaturated enamine upon a radical pathway and its key role within the catalytic cycle. Likewise, cobaltacycle **XX** was isolated and characterized by X-ray crystallography and the structure of cobalt complex **XXIII** was also confirmed by NMR spectroscopy. Based on these mechanistic experiments, they proposed a plausible reaction mechanism, wherein an electrophilic intermediate is initially formed under catalytic and oxidative reaction conditions (Scheme 18). Next, the latter would react with the Co(II) salt to deliver a Co(III) intermediate (**XIX**) prone to undergo the corresponding *ortho*-C–H functionalization event. Upon reaction with carbon monoxide and reductive elimination, the resulting intermediate **XXII** would be likely hydrolyzed to produce the product and release Co(III) catalyst **XXIII**, which can then again coordinate with the corresponding enamine.

Inspired by the work of Shi on the alkoxycarbonylation reactions with alkyl chloroformates as an alternative and safer C1 source,[49] Correa and co-workers have recently disclosed a scalable Pd-catalyzed C(sp^2)–H alkoxycarbonylation method of picolinamide-protected amines, including a variety of Phe derivatives.[50] Although the process often resulted in separable mixtures of mono- and difunctionalized compounds with a preferential formation of the dialkoxycarbonylated product when using natural Phe derivatives, the introduction of *ortho*- or *meta*-substituents within the aryl ring resulted in the exclusive mono-alkoxycarbonylated compounds (Scheme 19).

Interestingly, a Tyr derivative bearing the PA as DG could be also used. *In depth* Density Functional Theory calculations supported a Pd(II)/Pd(IV) catalytic cycle and provided valuable insights into the reaction mechanism. On the one hand, the role of *t*-amylOH as co-solvent was found key to decrease the energy profile upon coordination with the transient species, and on the other hand, the observed lack of reactivity of peptide derivatives was rationalized upon a competitive peptide backbone coordination. Based on the mechanistic studies, the proposed reaction pathway would start by coordi-



Scheme 18. Co-catalyzed carbonylation of Phe-containing peptides.



Scheme 19. C–H alkoxycarbonylation of Phe derivatives using PA as DG.

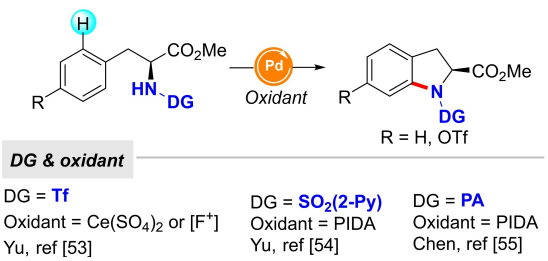
nation of the PA-Phe derivative with $Pd(OAc)_2$. After palladation and oxidative addition of the alkyl chloroformate, the ensuing Pd(IV) intermediate (**XXVI**) would undergo a reductive elimination step to provide a Pd(II) complex, which could either undergo the second alkoxycarbonylation event or provide the active Pd(II) catalyst upon reaction with the silver salt.

3. C–Heteroatom Bond-Forming Reactions

The direct conversion of a C–H bond into a C–Heteroatom bond represents a capital challenge in chemical synthesis. This section describes metal-catalyzed C(sp^2)–H functionalizations in which a heteroatom-containing motif is introduced into phenyl ring within Phe- and Tyr-containing compounds.

3.1. C–H Aminations

Owing to the prevalence of *N*-containing heterocycles in a plethora of medicinally relevant compounds, the development of new cyclization reactions is a pressing goal within modern chemistry. Despite the widespread use of Buchwald-Hartwig amination as a powerful tool for the assembly of heterocycles,[51] the parent processes featuring the direct amination of C–H bonds can occur in the presence of an oxidant in substrates devoid of a halide motif.[52] Palladium catalysis has enabled the conversion of a wide variety of conveniently *N*-protected β-arylethylamines into the corresponding indoline derivatives upon intramolecular oxidative C–H amination reactions. Among the substrates explored, simple Phe and Tyr derivatives have been also used to forge new C–N bonds at the δ-C–H site through the formation of the corresponding palladacycle. Early reports by Yu demonstrated the use of triflamide-protected Phe and Tyr compounds in combination with $Ce(SO_4)_2$ and *N*-fluoro-2,4,6-trimethylpyridinium triflate [F^+] as oxidant.[53] Subsequent studies by Yu[54] and Chen[55] enabled the use of $PhI(OAc)_2$ as an efficient oxidant with both 2-pyridinesulfonyl- and picolinamide-protected compounds, respectively (Scheme 20). Remarkably, the method by Chen on PA-protected Phe could be performed with even 0.5 mol% of $Pd(OAc)_2$ and it could be applied for the assembly a key building block within the synthesis of Betanin. Although full mechanistic studies were not disclosed, the reaction was proposed to occur through a Pd(II)/Pd(IV) catalytic



Scheme 20. Early reports on C–H aminations of Phe and Tyr derivatives.

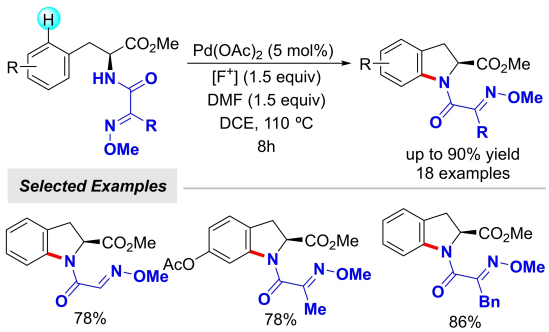
cycle entailing a sequence of C–H directed palladation and oxidation to a Pd(IV) intermediate, which eventually underwent a C–N bond-forming reductive elimination.

In 2015, the group of Ma disclosed a related intramolecular amination with 2-methoxyiminoacyl-protected Phe compounds.[56] This amination protocol enabled the assembly of a wide range of indoline derivatives in excellent yields, even those derived from O-protected Tyr derivatives (Scheme 21). Interestingly, a subsequent hydrogenation reaction of the DG (oxime motif) led to the corresponding dipeptides as diastereomeric mixtures.

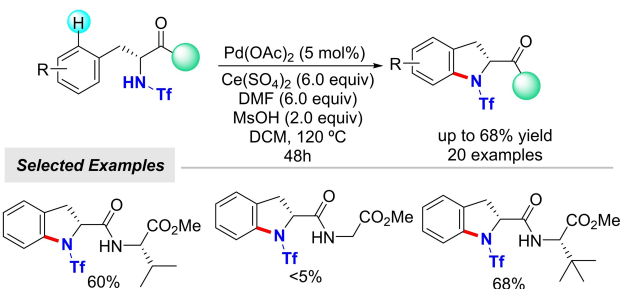
Prompted by the successful cyclization of simple triflamide-protected Phe compounds by Yu,[53] Shi and co-workers reported an intramolecular amination reaction with more complex Phe-containing dipeptides under similar reaction conditions involving the use of [F$^+$] as oxidant.[57] The nature of the adjacent amino acid residue had a determinant impact on the reaction outcome, and Tf-Phe-Gly-OMe resulted in just traces of the corresponding heterocyclic product. Conversely, amino acids housing a bulky substituent such as a *tert*-butyl group significantly enhanced the conversion and yield of the process (Scheme 22). The use of electron-rich Tyr-containing dipeptide resulted in the over-oxidized indole derivative.

As commented above, whereas the use of a DG represents one of the most common tactic within the field of C–H functionalization, the development of methods which harness the peptide backbone as an internal DG are highly desirable. In this light, Xuan and co-workers disclosed a complementary intramolecular amination reaction leveraging the peptide backbone to assist the intramolecular amination within dipeptides housing a *C*-terminal Phe unit.[58] Control experiments with dipeptides devoid of the NH bond such as tertiary amides underpinned the crucial role of the secondary amide to chelate with the metal catalyst. The method boded well with a number of amino acids such as protected Ser or Trp, among others. Furthermore, not only O-acetylated Tyr-dipeptides but also unnatural Phe compounds bearing halides and a nitro a group within the aryl ring underwent the corresponding intramolecular C–H amination in good yields. Based on existing precedents, a Pd(II)/Pd(IV) catalytic cycle was proposed (Scheme 23). Initial coordination of $Pd(OAc)_2$ with the dipeptide backbone would facilitate the formation of the corresponding palladacycle **XXIX**. The latter would undergo oxidative addition with PIDA to deliver a highly reactive Pd(IV) species (**XXX**), which would eventually result in the assembly of the heterocyclic compound upon a C–N bond-forming reductive elimination.

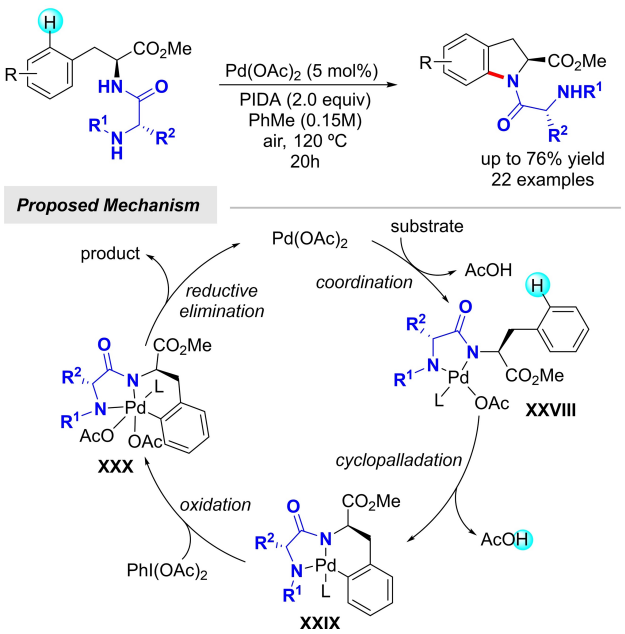
Very recently, Hoarau and co-workers performed mechanistic studies on the formation of indoline compounds from the corresponding free-amino-bounded palladacycles.[59] Following the procedure reported by Vicente and Saura-Llamas,[46] a series of Phe-derived 6-membered dimeric palladacycles (**XXXI**) were prepared. Upon coordination with the SPhos phosphine ligand, the corresponding monomeric species **XXXII** were formed. After careful screening of the base, solvent and temperature, they concluded that the latter could undergo the corresponding reductive elimination of Pd(0) to deliver the corresponding NH-free indoline in the presence of K_2CO_3 at 100 °C (Scheme 24). The nature of the counterion and phosphine ligand had a major impact on the reaction outcome. DFT studies supported the facile carbonate-assisted N–H activation prior to the reductive elimination event. Although these mechanistic studies do not rationalize the oxidative C–H aminations described above, they



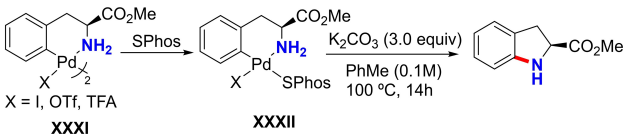
Scheme 21. C–H aminations using 2-methoxyiminoacyl-protected derivatives.



Scheme 22. C–H aminations of dipeptides using Tf as DG.



Scheme 23. Backbone-directed C–H amination of dipeptides.



Scheme 24. Base-assisted C–H amination of L-Phe-OMe.

could lay the foundation for performing analogous studies to understand the proposed Pd(II)/Pd(IV) regime when using Phe compounds housing a DG or the peptide backbone.

3.2. Miscellaneous Reactions

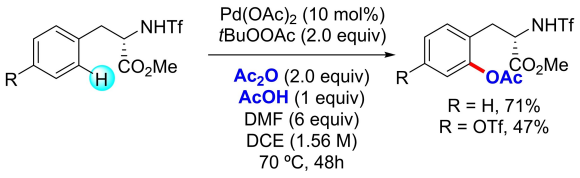
In connection with their work on the C–H functionalization of triflamide-protected β-arylethylamines, the group of Yu developed a Pd-catalyzed acetoxylation of a variety of phenethylamines including Tf-protected Phe and Tyr compounds (Scheme 25).[60] Interestingly, the resulting *ortho*-acetoxylated Phe derivative could further undergo an intramolecular C–H amination to assemble the corresponding *ortho*-acetoxylated indoline compound under previously described reaction conditons.[53]

Owing to their high synthetic versatility, the introduction of boronic esters into α-amino acids or peptides constitutes an important avenue toward the assembly of fully decorated biomolecules. In 2010, Meyer et al. designed a practical Ir-catalyzed C–H borylation with bis(pinacolato)diboron (B_2pin_2) of a collection of Boc-Phe-OMe compounds housing a number of substituents at the *meta* position[61] (Scheme 26). In general, the borylation preferentially occurred at the C5 site, and the parent 3,4-regioisomer was formed in very low yields, which was attributed to steric issues. In fact, the use of 2-chlorophenylalanine derivative resulted in the formation of a mixture of 2,4- and 2,5-isomers in almost 1:1 ratio, and the use of natural Boc-Phe-OMe ushered in a mixture of 3,4-, 3,5- and the corresponding diborylated compound. Therefore, the presence of a *meta* substituent clearly boosted the regioselectivity of the process. Notably, Elhammer and co-workers further applied this technique for the C–H borylation of the natural product Aureobasidin A, a cyclopeptide of high structural complexity bearing two distinct Phe residues.[62] Notably, the method was found selective toward the modification of the less sterically hindered Phe residue and delivered a mixture of *meta*- and *para*-isomers, which turned out to exhibit remarkable antifungal activity.

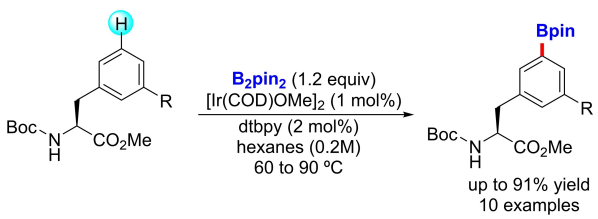
The group of Shi alternatively developed a very robust, yet general Pd-catalyzed C–H borylation method featuring the use of PA as efficient DG.[63] This method could be applied for the borylation of a number of amino acids at the C(sp^3)–H, but it was also shown applicable for the selective borylation of PA-Phe-OMe (Scheme 27).

In the experiments conducted by Vicente and co-workers on the *ortho*-palladation of L-Phe-OMe·HCl commented above,[46] the synthesis of 2-bromo and 2-iodophenylalanine methyl esters was demonstrated to occur from dimeric organopalladacycles upon treatment with bromine and iodine, respectively. However, the very first metal-catalyzed C–H halogenation reaction of simple Phe and Tyr compounds was reported by Yu in 2008.[25] In particular, they found that the use of triflamide as DG enabled the diiodination of both Phe and Tyr compounds in the presence of I_2 under oxidative reaction conditions (Scheme 28). The resulting iodinated amino acids could be further used for the assembly of the corresponding indoline derivatives upon a Cu-mediated intramolecular amination.

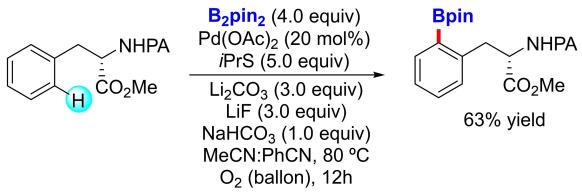
Barluenga and co-workers have extensively explored the iodination of both Phe- and Tyr-containing peptides under metal-free reaction conditions,[64] and these halogenated derivatives have been used as versatile building blocks for post-modification reactions including Suzuki[65] and Negishi[66] couplings. Despite the importance of these metal-free synthetic tools, they often led to mixtures of *ortho*- and *para*-iodinated amino acids. In this respect, inspired by the modifications on α-



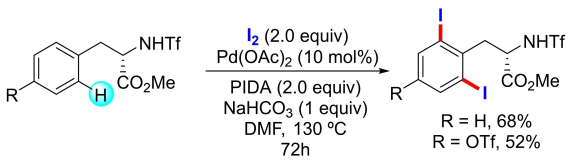
Scheme 25. C–H acetoxylation using Tf as DG.



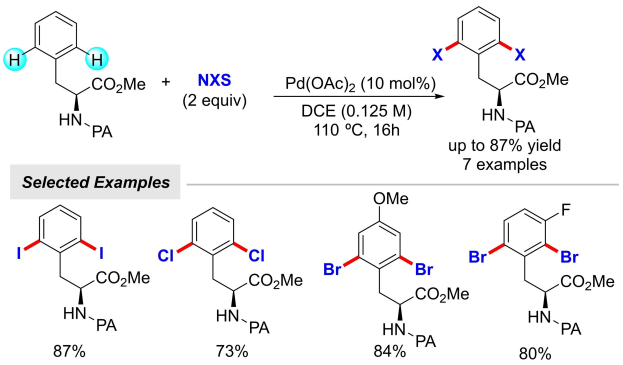
Scheme 26. Ir-catalyzed C–H borylation.



Scheme 27. C–H borylation using PA as DG.



Scheme 28. Pd-catalyzed C–H diiodination.



Scheme 29. Pd-catalyzed C–H dihalogenation.

phenylglycine compounds developed by Jiang and co-workers,[14] the group of Correa has recently reported the dihalogenation of a short family of picolinamide-protected Phe and Tyr compounds.[43] Upon the variation of the corresponding *N*-halosuccinimide, bromo, iodo and even chloro atoms could be installed at the aryl ring in excellent yields (Scheme 29).

4. Conclusions and Outlook

The development of reliable and sustainable synthetic tools to label proteinogenic amino acids within a peptide framework for the ultimate modification of proteins in a late-stage and site-selective fashion is rapidly growing importance within the realm of chemical biology. In particular, metal-catalyzed C–H functionalization reactions have lately opened up new horizons in the area of bioconjugation and constitute a straightforward avenue to assemble modified peptides that are beyond the reach of traditional methods. Although trivial at first sight, the direct translation of a given metal-catalyzed C–H functionalization reaction within a simple aryl system into the corresponding Phe- or Tyr-containing peptide represents a daunting challenge. Not only the peptide backbone itself but also the multiple functional groups within the sequence could deeply compromise the required coordination with the metal catalyst, thereby resulting in total inhibition of the desired transformation. Likewise, the presence of multiple chemically similar C–H bonds in a peptide compound often results in selectivity issues. As a result, the available C–H functionalization portfolio cannot be always extended from single amino acid residues to the corresponding short-to-medium peptides. This review details the currently available set of metal-catalyzed reactions for the modification of hydrophobic Phe and Tyr-containing compounds, classified by the nature of the corresponding bond-forming process. Despite the advances realized, the use of C–H functionalization has not reached yet its full synthetic potential within peptide chemistry, and several challenges need to be solved to improve the practicality of the existing protocols and design other innovative strategies. First, limited knowledge has been gathered regarding the mechanism of some of the metal-catalyzed events disclosed herein, which are often merely speculative and based on indirect experimental evidence. Therefore, the mechanistic understanding of the underlying elemental steps through isolation of the putative intermediates could certainly foster wider applications at the forefront of organometallic and peptide chemistry. Second, some of the reported protocols are not yet broadly applicable to native and large oligopeptides and relied on the use of fully protected single amino acid residues. Third, huge number of chemical oxidants and additives are often required, thus diminishing the sustainability of the protocols. In this respect, emerging trends such as the use of electricity could offer attractive opportunities for achieving biocompatible labelling reactions,[67] thereby avoiding the use of chemical oxidants and byproducts derived thereof. Finally, owing to the chemical versatility of the resulting products, the development of new reactions to install heteroatom-containing motifs into the peptide template represents a task of prime importance. In summary, we anticipate that efforts along these lines could have a significant impact on the use of metal-catalyzed C–H functionalizations as an enabling tool toward the late-stage modification of peptides, and we hope that this review could serve as a practical user guide, while inspiring practitioners in the field to seek for novel tagging reactions in the years to come.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–H functionalization · Homogeneous catalysis · Late-stage modification · Peptides · Phenylalanine · Tyrosine

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